REMARKS

Applicant respectfully requests reconsideration. Claims 87-119 were previously pending in this application. Claims 87 and 118 have been amended. Claim 87 has been amended to remove the phrase "individual, purified" in step (a) to simplify the claim language to simplify the claim language. Claim 87 has also been amended to clarify the claim by indicating that in step (b) the non-aqueous lipid solution of step (a) is contacted with a second non-aqueous solvent resulting in the at least two phospholipids precipitating out as a solid lipid blend. Claims 93-97 and 118 have been amended to include the word "contains". Support for the amendment can be found in the specification as originally filed at least at page 15, lines 13, 15, 24-25, and in the examples at page 24. Claim 118 has also been amended to remove the word "purified" to ensure correct antecedent basis. As a result, claims 87-119 are pending for examination with claim 87 being an independent claim. No new matter has been added.

Non-rejected claims

Applicant submits that the Examiner provided no basis or explanation for the rejection of claims 118 and 119 in the Office Action mailed April 16, 2010. Applicant requests that the Examiner indicate that the claims are in condition for allowance or if they are to be rejected, provide a rational and basis for their rejection. If claims 118 and 119 are rejected in a subsequent Office Action, Applicant submits that the rejection at that time would be the first rejection of those claims.

Rejections under 35 U.S.C. §112

Claims 87-117 are rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. Applicant respectfully disagrees with the Examiner's contention that the specification does not support the use of purified phospholipids. The description of the phospholipids in the specification indicates that the lipids can be what is art-recognized as "pure". For example, at page 22, the phospholipids are described as having certificates of analysis, which would indicate to one of ordinary skill in the art that phospholipids used in the claimed methods could be phospholipids that meet standards for pharmaceutical manufacturing and thus would be considered to be "pure". Based on the teaching in the specification it is unnecessary to

indicate in claim 87 that the phospholipids are "purified phospholipids" because reading the specification would lead one of ordinary skill in the art to understand that purified phospholipids could be used. Therefore, Applicant has amended the claims to remove the phrase.

Accordingly, withdrawal of the rejection of claims 87-117 under 35 U.S.C. §112, first paragraph is respectfully requested.

Claims 87-117 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicant respectfully disagrees with the Examiner's conclusion that claim 87 is indefinite because the percentage of purification of the phospholipids is unclear. As discussed above, Applicant has removed the term "purified" from claim 87 because its inclusion is not necessary in order for one of skill in the art to understand that purified phospholipids could be used in methods of the invention. The removal of the term renders moot the rejection of claims 87-115 under 35 U.S.C. §112, second paragraph, as indefinite.

Accordingly, withdrawal of the rejection of claims 87-117 under 35 U.S.C. §112, second paragraph is respectfully requested.

Rejections Under 35 U.S.C. §103

Claims 87-111 and 117 are rejected under 35 U.S.C. §103(a) as being unpatentable over Nyberg (5,677,472) in view of Kissel (4,863,740) or Papahadjopoulos (4,235,871) or Lenk (4,522,803) or Kikuchi (4,687,661) individually or in combination. Applicant respectfully traverses the rejection.

The Examiner stated at page 2 of the previous Office Action mailed August 13, 2009, that "In view of Applicant's arguments, Unger (6,521,211) is removed from the rejections." In response to the Office Action mailed August 13, 2009 Applicant requested that references to the Unger '211 patent be removed from the rejection. Applicant notes that at page 3 of the Office Action mailed April 16, 2010, the Examiner again states that "Nyberg et al. and Unger teach steps a, b, and c" of the instant claim 87. Applicant believes inclusion of the Unger '211 patent in the body of the

rejection to be in error, and based on this understanding, presents no arguments regarding the Unger '211 patent in response to the instant rejection. Applicant respectfully requests clarification.

With respect to the issues raised in the remainder of the rejection, the Examiner asserts that Nyberg discloses methods of preparing phospholipid precipitates and states at page 3 of the Office Action mailed April 16, 2010, that Nyberg et al. "specifically indicate separation of phospholipids into different phases (column 5, lines 53-57; example 1, lines 56-67; and example 2)". Applicant submits that this teaching clearly distinguishes Nyberg et al. from the instant invention set forth in claims 87-111 and 117 and fails to support the rejection. In claim 87, the blend of the at least two phospholipids of (a) is precipitated out as a blend by contacting the non-aqueous solution of (a) with a second non aqueous solvent in step (b).

Independent claim 87 includes steps of combining at least two phospholipids into a blend of the at least two phospholipids. The at least two phospholipids of claim 87 begin as separate phospholipids and are combined in step (a)and precipitated out as a blend in step (b). The resulting solid collected in step (c) is a blend of the phospholipids that were combined, and there is no separation of the phospholipids from each other. Based on the claims and the teaching in the instant specification, it would be understood by one of ordinary skill in the art that the process of claim 87 results in a blend of the two or more phospholipids.

The result of steps (a) – (c) of claim 87 would be in direct contrast with the outcome of the Nyberg et al. teaching. As concluded by the Examiner, Nyberg et al. teaches separating out lipids from naturally occurring mixtures thus resulting in lipids that are separate from each other. As stated by the Examiner, at page 3, Nyberg teaches a starting material that is a "phospholipids blend" that is exposed to solutions to separate out the phospholipids from the mixture into different phases. Clearly this does not yield a blend of the phospholipids. The Examiner's conclusion that the separation of phospholipids from each other into separate phases by Nyberg et al. as teaching steps a, b, and c of claim 87 is incorrect. From the Examiner's assertion that Nyberg et al. "specifically indicates separation of phospholipids into different phases" one must conclude that Nyberg et al. fails to teach or suggest mixing together individual, separate phospholipids to make a lipid blend and therefore, fails to teach steps (a) – (c) of claim 87.

For the rejection of claims 87-111 and 117 the Examiner relies on the secondary references, Kissel et al., Kikuchi et al., Papahadjopoulos et al., or Lenk et al., as teaching or suggesting any of steps (d) and (e) of claim 87, but does not rely on these secondary references as teaching or suggesting steps (a) – (c) of claim 87. At pages 3-4 of the Office Action mailed April 16, 2010, the Examiner states that Kissel, Papahadjopoulos, Lenk, and Kikuchi describe preparing liposomes, and in each case the method is to dissolve a phospholipid in a non-aqueous solvent followed by addition of an aqueous solvent. None of the secondary references teaches or suggests steps (a) – (c) of claim 87 and combining the methods set forth in the cited references would not result in a lipid suspension comprising phospholipid particles as claimed.

The Examiner states at page 8 of the Office Action "irrespective of how many times the mixture is precipitated, when it is finally dissolved in a non-aqueous solvent, the phospholipid mixture would be the same in a dissolved state compared to two phospholipids added directly into a non-aqueous solvent so as to dissolve them." Applicant submits that this statement is incorrect and mischaracterizes the claimed method. A basis of the claimed invention is Applicant's discovery of a method that yields an improved product. The resulting product is not the same as would be prepared without steps (a) – (c) of claim 87. As described in the Declaration under 37 C.F.R. under §1.132 by Dr. Mark Watson, the inclusion of steps (a) – (c) of claim 87 is critical for the preparation of the claimed lipid suspension and the resulting suspension is significantly different than a suspension that would result without inclusion of these steps. Each of the claimed steps is important to permit preparation of a uniform phospholipid blend of the claimed invention. The steps as claimed are critical to circumvent difficulties encountered using alternative methods. Such difficulties, as outlined at page 2 of the specification as filed, include lack of uniformity, lack of purity, difficulty in recovery of solids, etc.

The Examiner concludes at pages 7, last paragraph, through page 8 of the Office Action that even without steps (a) – (c) of claim 87, the resulting lipid solution would be the same. Applicant disagrees with this assessment. As disclosed in the specification, the inclusion of steps (a) – (c) of claim 87 permits preparation of a uniform phospholipid suspension of the at least two phospholipids and results in more uniform particle size because of the additional steps. This conclusion is also supported by the Declaration under 37 C.F.R under §1.132 by Dr. Mark Watson,

submitted herewith. The declaration indicates that difficulties with prior methods of preparing phospholipid suspensions had included lack of uniformity and difficulty in preparing suspensions with uniform blends of phospholipids and uniform lipid particle sizes. The solution for this difficulty was not recognized until it was identified by Applicant. As stated in the Declaration, Applicant attempted a number of different strategies to overcome difficulties Applicant identified as resulting with alternative methods and was surprised that the strategy set forth in steps (a) – (c) of claim 87 successfully yielded an improved, uniform phospholipid suspension.

The Examiner has based the rejection, in part, on a conclusion that one skilled in the art would add the two additional steps of dissolving previously separate phospholipids in three different non-aqueous solvents to make a lipid blend. None of the cited references, either alone or in combination, teaches or suggests inclusion of these steps, which are critical to the methods as claimed. Therefore, the combination of references fails to provide a basis for the obviousness rejection because each element of the invention as claimed is not taught or suggested by the combination and also, and the Examiner has provided no "apparent reason to combine the known elements in the fashion claimed." *KSR Int'l Co. v. Teleflex, Inc.*, 550; 421 U.S. 398 (2007). The Examiner's conclusion of obviousness appears to be based on the impermissible application of hindsight reasoning. A *prima facie* case for obviousness has not been made.

Additional support for a finding of non-obviousness is provided in the Declaration by Dr. Mark Watson, which provides evidence of commercial success of a product made using the claimed method. There is a well established nexus between the claimed invention and the commercial success of a phospholipid suspension imaging agent product, which is sold in the United States and abroad under the name Definity®. The ability to prepare a uniform lipid suspension of the at least two phospholipids is dependent on the use of the methods set forth in claim 87. Thus, the commercial success of the Definity® product is commensurate with the scope of the independent claim 87 and flows from the functions and advantages disclosed and inherent in the description in the specification. The Definity® product has been commercially successful both in the United States. and abroad. As indicated in *Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co.*, 730 F.2d 1452, 221 USPQ 481 (Fed. Cir. 1984) commercial success abroad as well as that in the United States is relevant in support of a finding of non-obviousness.

The combination of the teaching of the primary reference, Nyberg et al., with any one or a combination of Kissel et al., Kikuchi et al., Papahadjopoulos et al., and Lenk et al. fails to teach each element of the invention as claimed and the combination of the teaching does not result in the claimed invention. The combination of references fails to support a *prima facie* case of obviousness. In addition, Applicant has indicated a clear nexus between the claimed invention and the commercial success of the Definity® product. Accordingly, Applicant respectfully requests reconsideration and withdrawal of the rejection of claims 87-111, and 117 under 35 U.S.C. §103(a), as unpatentable over Nyberg et al. in view of Kissel et al., Papahadjopoulos et al., Lenk et al., and Kikuchi et al., individually or in combination.

Claims 111-114 are rejected under 35 U.S.C. §103(a) as being unpatentable over Nyberg (5,677,472) in view of Kissel (4,863,740) or Papahadjopoulos (4,235,871) or Lenk (4,522,803) or Kikuchi (4,687,661) individually or in combination, further in view of Swaerd-Nordmo (6,165,442). Applicant respectfully traverses the rejection.

The rejected claims 111-114 ultimately depend from claim 87. As discussed above, Applicant submits that each element of claim 87, as amended, are not taught or suggested by the combination of Nyberg et al., in view of Kissel et al., Kikuchi et al., Papahadjopoulos et al., and Lenk et al. The addition of the teaching of Swaerd-Nordmo et al. to the combination does not remedy the deficit.

The Examiner states at pages 9-10 of the Office Action, that the Swaerd-Nordmo reference is combined for its teaching of encapsulating ultrasound contrast agents and that "steps a-c are obvious over the combination of Nyberg with the secondary references." As set forth above, the combined teaching of Nyberg et al., Kissel et al., Kikuchi et al., Papahadjopoulos et al., and/or Lenk et al. fails to teach or suggest a process that includes steps (a) to (c) of the invention as claimed, which result in a uniform blend of the at least two phospholipids. The addition of the teaching of Swaerd-Nordmo et al. to the combination fails to remedy the deficit. The combined references fail to teach or suggest each element of the claimed invention and a *prima facie* case for obviousness has not been established. Evidence of commercial success as set forth in the Declaration by Dr. Mark Watson also weighs against a finding of obviousness.

Accordingly, Applicant requests reconsideration and withdrawal of the rejection of claims 111-114 under 35 U.S.C. §103(a) as unpatentable over Nyberg in view of Kissel or Papahadjopoulos or Lenk or Kikuchi, individually or in combination, further in view of Swaerd-Nordmo.

Claims 115 and116 are rejected under 35 U.S.C. §103(a) as being unpatentable over Nyberg (5,677,472) in view of Kissel (4,863,740) or Papahadjopoulos (4,235,871) or Lenk (4,522,803) or Kikuchi (4,687,661) individually or in combination, in view of Swaerd-Nordmo, further in view of Unger (6,071,495). Applicant respectfully traverses the rejection.

Rejected claims 115-116 depend from claim 112, and ultimately depend from claim 87. As discussed above, each element of claim 87, as amended, are not taught or suggested by the combination of Nyberg et al., in view of Kissel et al., Kikuchi et al., Papahadjopoulos et al., and Lenk et al. in view of Swaerd-Nordmo et al. Addition of the teaching of Unger to the combination does not remedy the deficit.

The Examiner states at page 10 of the Office Action, that the Unger et al., reference "is combined for its teachings of sterilization" and that "steps a-c are obvious over the combination of Nyberg et al. with the secondary references". As set forth above, the combined teaching of Nyberg et al., Kissel et al., Kikuchi et al., Papahadjopoulos et al., and/or Lenk et al. fails to teach or suggest any process that includes steps (a) to (c) of the invention as claimed, which result in a uniform blend of the at least two phospholipids. The addition of the teaching of Unger et al. to the combination of references does not remedy the deficit. The combination fails to teach or suggest each element of the claimed invention and a *prima facie* case for obviousness has not been established. Evidence of commercial success as set forth in the Declaration by Dr. Mark Watson also weighs against a finding of obviousness.

Accordingly, Applicant respectfully requests reconsideration and withdrawal of the rejection of claims 115-116 under 35 U.S.C. §103(a) as unpatentable over Nyberg in view of Kissel or Papahadjopoulos or Lenk or Kikuchi, individually or in combination, in view of Swaerd-Nordmo, further in view of Unger.

Claim 117 is rejected under 35 U.S.C. §103(a) as being unpatentable over Nyberg (5,677,472) in view of Kissel (4,863,740) or Papahadjopoulos (4,235,871) or Lenk (4,522,803) or Kikuchi (4,687,661) individually or in combination, further in view of Unger (6,416,740). Applicant respectfully traverses the rejection.

Rejected claim 117 ultimately depends from claim 87. As discussed above, each element of claim 87, as amended, are not taught or suggested by the combination of Nyberg et al., in view of Kissel et al., Kikuchi et al., Papahadjopoulos et al., and Lenk et al. Addition of the teaching of Unger to the combination does not remedy the deficit.

The Examiner states at page 11 of the Office Action, that the Unger et al., reference is combined for its teachings the claimed combination of phospholipids" and that that "steps a-c are obvious over the combination of Nyberg et al. with the secondary references". As argued above, the combination of the teaching of Nyberg et al., with Kissel et al., Kikuchi et al., Papahadjopoulos et al., and Lenk et al. fails to teach or suggest any process that includes steps (a) to (c) of the invention as claimed, which result in a uniform blend of the at least two phospholipids. The addition of the teaching of Unger et al. to the combination fails remedy the deficit, resulting in a failure to support a *prima facie* case for obviousness. Evidence of commercial success as set forth in the Declaration by Dr. Mark Watson also weighs against a finding of obviousness.

Accordingly, Applicant requests reconsideration and withdrawal of the rejection of claim 117 under 35 U.S.C. §103(a) as unpatentable over Nyberg in view of Kissel or Papahadjopoulos or Lenk or Kikuchi, individually or in combination, further in view of Unger.

Claims 87-111 are rejected under 35 U.S.C. §103(a) as being unpatentable over Kissel (4,863,740) or Papahadjopoulos (4,235,871) or Lenk (4,522,803) or Kikuchi (4,687,661) individually or in combination. Applicant respectfully traverses the rejection.

The Examiner at page 12 of the Office Action states "in essence" the Kissel et al., Papahadjopoulos et al., Lenk et al., or Kikuchi et al. references "teach steps d and e of claim 87." The Examiner then concludes that "instant steps a-c in claim 87 just recite re-precipitation of the lipids used in the formation of lipid suspension." Applicant respectfully disagrees with the Examiner's characterization.

As disclosed in the specification, the inclusion of steps (a) – (c) of claim 87 permits preparation of a uniform phospholipid suspension of the at least two phospholipids and results in more uniform particle size because of the additional steps – thus distinguishing the resulting product that one prepared using alternative methods. This conclusion is also supported by the statements and evidence provided in the Declaration under 37 C.F.R. §1.132 submitted herewith. The Declaration by Dr. Mark Watson indicates that difficulties with prior methods of preparing phospholipid suspensions had included lack of uniformity and difficulty in preparing suspensions with uniform blends of phospholipids and uniform lipid particle sizes. The solution for this difficulty was not recognized until it was identified by Applicants. As stated in the Declaration, Applicants attempted a number of different strategies to overcome the prior difficulties and were surprised that the strategy set forth in steps (a) – (c) of claim 87 successfully yielded an improved, uniform phospholipid suspension. As stated in the Declaration, steps (a) - (c) of claim 87 are critical to obtaining uniformity in the size of the particles of the lipid suspension made from the lipid blend, and thus are necessary steps in the process as claimed.

The specification as filed teaches the novel steps of combining at least two phospholipids together in a first non-aqueous solvent in which they dissolve and contacting the combined phospholipids with a second non-aqueous solvent that precipitates out both of the blended phospholipids together as a blend. This permits one skilled in the art to prepare a uniform lipid blend of the at least two phospholipids that results in enhanced characteristics of the prepared lipid suspension, characteristics that differ from lipid suspensions prepared without steps (a) – (c) as claimed. A lipid suspension resulting from the claimed process is a more uniform suspension and has a uniform particle size, than one prepared using the prior cited methods.

In addition, the inclusion of steps (a) – (c) in claim 87 is based on the discovery by Applicants that these steps unexpectedly resulted in an improved lipid suspension. The combined teaching in the cited references and the knowledge in the art at the time of filing would have not provided one skilled in the art with any reason or motivation to perform the additional dissolution and precipitation steps (a-c) to make a lipid blend as part of a process to make a lipid suspension. In fact, it would not have been reasonable for one skilled in the art to include steps (a) – (c) as purification steps when preparing a lipid suspension from separate phospholipids. Including such a

purification process would have been expected by one skilled in the art to result in a reduced yield and/or higher production costs, which would have been undesirable.

The inclusion of steps (a) – (c) are critical in the invention as claimed because Applicants understood that steps (a) – (c) were not purification steps, but rather served to increase the uniformity and particle size uniformity of the resulting phospholipid suspension. This benefit would not have been recognized or understood by one of ordinary skill in the art based on the teaching of the Kissel et al., Papahadjopoulos et al., Lenk et al., or Kikuchi et al. references, or based on knowledge in the art at the time of filing.

The Kissel et al., Papahadjopoulos et al., Lenk et al., and Kikuchi et al. references all fail to teach or suggest steps (a) – (c) of claim 87. As indicated in the Declaration of Dr. Mark Watson, steps (a) – (c) are critical to the invention as claimed to result in a uniform blend of the at least two phospholipids. The inclusion of steps (a) – (c) yields the unexpected result of a lipid suspension that has improved uniformity and more uniform particle size. The teachings of Kissel et al., Papahadjopoulos et al., Lenk et al., or Kikuchi et al. would not lead one to arrive at the instantly claimed invention – and the invention as claimed is not rendered obvious by the combined or individual cited references.

Additional support for a finding of non-obviousness is provided in the Declaration by Dr. Mark Watson, which provides evidence of commercial success of a product made using the claimed method. There is a well established nexus between the claimed invention and the commercial success of a phospholipid suspension imaging agent product, which is sold in the United States and abroad under the name Definity®. The ability to prepare a uniform lipid suspension of the at least two phospholipids is dependent on the use of the methods set forth in claim 87. Thus, the commercial success of the Definity® product is commensurate with the scope of the independent claim 87 and flows from the functions and advantages disclosed and inherent in the description in the specification. The Definity® product has been commercially successful both in the United States. and abroad. As indicated in *Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co.*, 730 F.2d 1452, 221 USPQ 481 (Fed. Cir. 1984) commercial success abroad as well as that in the United States is relevant in support of a finding of non-obviousness.

Accordingly, Applicant requests reconsideration and withdrawal of the rejection of claims 87-111 under 35 U.S.C. §103(a) as being unpatentable over Kissel (4,863,740) or Papahadjopoulos (4,235,871) or Lenk (4,522,803) or Kikuchi (4,687,661) individually or in combination.

Claim 117 is rejected under 35 U.S.C. §103(a) as being unpatentable over Kissel (4,863,740) or Paphadjopoulos (4,235,871) or Lenk (4,522,803) or Kikuchi (4,687,661) individually or in combination as set forth above, further in view of Unger (6,416,740). Applicant respectfully traverses the rejection.

Rejected claim 117 ultimately depends from claim 87. As discussed above, each element of claim 87, as amended, is not taught or suggested by the combination of teachings of, or individual teaching provided by, Kissel et al., Kikuchi et al., Papahadjopoulos et al., or Lenk et al. Addition of the teaching of Unger to the combination does not remedy the deficit. Evidence of commercial success as set forth in the Declaration by Dr. Mark Watson also weighs against a finding of obviousness.

The Examiner states at page 14 of the Office Action that the Unger et al., reference "is combined for its teachings of art known use of the claimed combination of the phospholipids." As argued above, Kissel et al., Kikuchi et al., Papahadjopoulos et al., and/or Lenk et al., alone and in combination, fail to teach or suggest any process that includes steps (a) – (c) of claim 87. As stated in the Declaration of Dr. Mark Watson, steps (a) - (c) of claim 87 are critical to obtaining uniformity in the size of the particles of the lipid suspension made from the lipid blend, and are necessary steps in the process as claimed.

As set forth above, steps (a) – (c) are critical steps in the claimed process. Combining two or more individual, separate phospholipids with non-aqueous solvents to prepare a lipid blend, dissolving that blend in a non-aqueous solution, and mixing the dissolved blend into an aqueous solution, are not taught or suggested by Kissel et al., Kikuchi et al., Papahadjopoulos et al., or Lenk et al. The lack of teaching or suggestion of elements of the invention as claimed supports a conclusion of non-obviousness over the cited art. The addition of the teaching of Unger et al. to the teaching of the individual Kissel et al., Kikuchi et al., Papahadjopoulos et al., or Lenk et al

references, of any combination thereof, also fails to teach or suggest each element of the claimed invention and fails to support a *prima facie* case for obviousness.

Accordingly, Applicant requests reconsideration and withdrawal of the rejection of claim 117 under 35 U.S.C. §103(a) as unpatentable over Kissel or Papahadjopoulos or Lenk or Kikuchi, individually or in combination, further in view of Unger.

Claims 87-111 and 117 are rejected under 35 U.S.C. §103(a) as being unpatentable over Munechika (5,662,931) in combination with Kissel (4,863,740) or Papahadjopoulos (4,235,871) or Lenk (4,522,803) or Kikuchi (4,687,661) individually or in combination. Applicant respectfully traverses the rejection.

The Examiner states at page 14 of the Office Action that Munechika discloses a method of preparing liposomes that includes "dissolving the lipids in an organic solvent, precipitating the lipids using a second organic solvent and hydrating the precipitate with an aqueous solution to form liposomes (col. 2, line 8 through col. 3, line 61 and examples)." The Examiner's characterization of the Munechika et al. disclosure is not correct. Munechika describes making an emulsion that includes steps of dissolving a lipid in a first organic solvent that is immiscible in water – followed by adding a "drug-containing aqueous solution" to the dissolved lipid and forming an emulsion (see abstract and col. 2, lines 63 to col. 3 line 2.) The process taught by Munechika et al. includes placing a drug into an aqueous solvent and adding that aqueous mixture to the first organic solvent in which the lipids are dissolved – forming an organic/aqueous emulsion. Munechika further discloses that the organic/aqueous emulsion can then be added to a second organic solvent, and then to a second aqueous solvent.

The Examiner's characterization of the process taught by Munechika et al. omits Munechika's step of adding an aqueous solvent to the first organic solvent in which water is immiscible. The process of Munechika is significantly different than the process as claimed in claim 87 as amended and is not suggestive of the instantly claimed process. The process taught in Munechika appears more similar to that of Kissel et al., Kikuchi et al., Papahadjopoulos et al., and/or Lenk et al. in that it includes contact with a single non-aqueous solvent followed by contact with an aqueous solvent. The processes taught by Munechika, Kissel et al., Kikuchi et al.,

Papahadjopoulos et al., and Lenk each omits the critical steps of (a) – (c) of claim 87 and do not render obvious the invention as claimed. As set forth in the Declaration by Dr. Mark Watson, steps (a) – (c) of claim 87 are critical and that criticality was identified by Applicant. One of ordinary skill in the art would not have any reason to add steps (a) – (c) based on combined teaching of the cited references as there was no recognition of the improvement of uniformity of the phospholipid blend and particle size in a lipid suspension until the claimed methods were identified by Applicant.

At page 16 of the Office Action, the Examiner contends that the comprising language of claim 87 does not exclude the inclusion of water to form an emulsion in the claimed method and states that "Munechika essentially teaches the precipitation of the lipid mixture, followed by dissolving in an organic solvent and the additional of aqueous solution." Applicant disagrees with the Examiner's interpretation but to improve clarity of the claims has amended step (b) of claim 87 to indicate that the non-aqueous solution of step (a) is the non-aqueous solution to which a second non-aqueous solvent is added in step (b). Any addition of water to the solution of step (a) prior to contact with the second non-aqueous solvent in step (b) would be excluded.

One skilled in the art could not combine the disclosure of Munechika with that of Kissel et al., Kikuchi et al., Papahadjopoulos et al., and/or Lenk et al. to arrive at the instantly claimed invention and also would also have no motivation to combine the references to make the invention as claimed. The combined teaching of Munechika et al and that of Kissel et al., Kikuchi et al., Papahadjopoulos et al., and/or Lenk et al. does not render obvious the claimed invention.

Additional support for a finding of non-obviousness is provided in the Declaration by Dr. Mark Watson, which provides evidence of commercial success of a product made using the claimed method. There is a well established nexus between the claimed invention and the commercial success of a phospholipid suspension imaging agent product, which is sold in the United States and abroad under the name Definity®. The ability to prepare a uniform lipid suspension of the at least two phospholipids is dependent on the use of the methods set forth in claim 87. Thus, the commercial success of the Definity® product is commensurate with the scope of the independent claim 87 and flows from the functions and advantages disclosed and inherent in the description in the specification. The Definity® product has been commercially successful both in the United States. and abroad. As indicated in *Lindemann Maschinenfabrik GMBH v. American Hoist &*

Derrick Co., 730 F.2d 1452, 221 USPQ 481 (Fed. Cir. 1984) commercial success abroad as well as that in the United States is relevant in support of a finding of non-obviousness.

Accordingly, Applicant requests reconsideration and withdrawal of the rejection of claims 87-111 and 117 under 35 U.S.C. §103(a) as unpatentable over Munechika in combination with Kissel or Papahadjopoulos or Lenk or Kikuchi, individually or in combination.

Claims 112-114 are rejected under 35 U.S.C. §103(a) as being unpatentable over Munechika (5,662,931) in combination with Kissel (4,863,740) or Papahadjopoulos (4,235,871) or Lenk (4,522,803) or Kikuchi (4,687,661) individually or in combination as set forth above, further in view of Swaerd-Nordmo (6,165,442). Applicant respectfully traverses the rejection.

Rejected claims 112-114 ultimately depend from claim 87. As discussed above, each element of claim 87, as amended, are not taught or suggested by the combination of Munechika et al., in view of Kissel et al., Papahadjopoulos et al., Lenk et al., or Kikuchi et al. The addition of the teaching of Swaerd-Nordmo et al. to the combination does not remedy the deficit.

The Examiner indicates at page 16 of the Office Action, that the Swaerd-Nordmo reference teaches "exchanging air with perfluorohydrocarbons in a vacuum chamber." As set forth above, Munechika et al. teaches a process with steps of contacting a lipid with an organic solvent that is immiscible in water, then contacting the mixture with an aqueous solvent/drug solution to form an emulsion. This teaching differs substantially from the instantly claimed invention and fails to teach or suggest any process that includes steps (a) – (c) of claim 87 as amended, which results in a uniform blend of phospholipids as further evidenced by the Declaration of Dr. Mark Watson. The combination of the teaching of Munechika et al., Kissel et al., Papahadjopoulos et al., Lenk et al., and/or Kikuchi et al., fails to teach or suggest each element of the claimed invention and the addition of the teaching of Swaerd-Nordmo et al. to the combination fails to remedy the deficit and a *prima facie* case for obviousness has not been established. Evidence of commercial success as set forth in the Declaration by Dr. Mark Watson also weighs against a finding of obviousness.

Accordingly, Applicant requests reconsideration and withdrawal of the rejection of claims 112-114 under 35 U.S.C. §103(a) as unpatentable over Munechika in combination with Kissel or

Papahadjopoulos or Lenk or Kikuchi, individually or in combination in view of Swaerd-Nordmo (6,165,442).

Claims 115-116 are rejected under 35 U.S.C. §103(a) as being unpatentable over Munechika (5,662,931) in combination with Kissel (4,863,740) or Papahadjopoulos (4,235,871) or Lenk (4,522,803) or Kikuchi (4,687,661) individually or in combination in view of Swaerd-Nordmo (6,165,442) as set forth above, further in view of Unger (6,071,495). Applicant respectfully traverses the rejection.

Rejected claims 115-116 ultimately depend from claim 87. As discussed above, each element of claim 87, as amended, are not taught or suggested by the combination of Munechika et al., in combination with Kissel et al., Papahadjopoulos et al., Lenk et al., or Kikuchi et al., and in view of Swaerd-Nordmo et al. The addition of the teaching of Unger et al., to the combination does not remedy the deficit.

The Examiner indicates at page 17 of the Office Action, that the Unger et al. reference teaches "final sterilization of the product." Applicant submits that, as argued above, Munechika et al. teaches a process that, in part, includes steps of contacting a lipid with an organic solvent that is immiscible in water, then contacting the mixture with an aqueous solvent/drug solution to form an emulsion. This teaching differs substantially from the instantly claimed invention set forth and fails to teach or suggest any process that includes steps (a) – (c) of claim 87 as amended, which results in a uniform blend of phospholipids. As argued above, the combination of the teaching of Munechika et al., Kissel et al., Papahadjopoulos et al., Lenk et al., and/or Kikuchi et al., and Swaerd-Nordmo et al. fails to teach or suggest each element of the invention as claimed. The addition of the teaching of Unger et al. does not result in a combination that teaches or suggests each element of the claimed invention. A *prima facie* case for obviousness is not supported. Evidence of commercial success as set forth in the Declaration by Dr. Mark Watson also weighs against a finding of obviousness.

Accordingly, Applicant requests reconsideration and withdrawal of the rejection of claims 115-116 under 35 U.S.C. §103(a) as unpatentable over Munechika in combination with Kissel or Papahadjopoulos or Lenk or Kikuchi, individually or in combination in view of Swaerd-Nordmo, as set forth above, further in view of Unger.

Claim 117 is rejected under 35 U.S.C. §103(a) as being unpatentable over Munechika (5,662,931) in combination with Kissel (4,863,740) or Papahadjopoulos (4,235,871) or Lenk (4,522,803) or Kikuchi (4,687,661) individually or in combination as set forth above, further in view of Unger (6,416,740). Applicant respectfully traverses the rejection.

Rejected claim 117 ultimately depends from claim 87. As discussed above, each element of claim 87, as amended, are not taught or suggested by the teaching of Munechika et al. in combination with Kissel et al., or Papahadjopoulos et al., or Lenk et al., or Kikuchi et al. The addition of the teaching of Unger et al., to the combination does not remedy the deficit.

The Examiner indicates at page 18 of the Office Action, that the Unger et al. reference teaches use of a combination of DPPA, DPPE-PEG5000 and DPPC in liposome preparation. The Unger et al. reference, however, does not teach the preparation of a phospholipid blend using instant steps (a) – (c) of claim 87 as amended. As set forth above, Munechika et al. teaches a process that, in part, includes steps of contacting a lipid with an organic solvent that is immiscible in water, then contacting the mixture with an aqueous solvent/drug solution to form an emulsion. This teaching differs significantly from the instantly claimed invention set forth and fails to teach or suggest any process that includes steps (a) – (c) of claim 87 as amended, which results in a uniform blend of phospholipids. As set forth above, the combination of the teaching of Munechika et al. with Kissel et al. or Papahadjopoulos et al. or Lenk et al. or Kikuchi et al. does not teach or suggest each element of the claimed invention. The addition of the teaching of Unger et al. does not result in a combination that teaches or suggests each element of the claimed invention. A *prima facie* case for obviousness has not been established. Evidence of commercial success as set forth in the Declaration by Dr. Mark Watson also weighs against a finding of obviousness.

Accordingly, Applicant requests reconsideration and withdrawal of the rejection of claim 117 under 35 U.S.C. §103(a) as unpatentable over Munechika in combination with Kissel or Papahadjopoulos or Lenk or Kikuchi, individually or in combination as set forth above, further in view of Unger 6,416,740.

CONCLUSION

A Notice of Allowance is respectfully requested. The Examiner is requested to call the undersigned at the telephone number listed below if this communication does not place the case in condition for allowance.

If this response is not considered timely filed and if a request for an extension of time is otherwise absent, Applicant hereby requests any necessary extension of time. If there is a fee occasioned by this response, including an extension fee, the Director is hereby authorized to charge any deficiency or credit any overpayment in the fees filed, asserted to be filed or which should have been filed herewith to our Deposit Account No. 23/2825, under Docket No. N0469.70022US02.

Dated: October 18, 2010

Respectfully submitted,

By _____

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